

The Gynecologic Cancer Intergroup (GCIG): history and current status

J. B. Vermorken^{1*}, E. Avall-Lundqvist², J. Pfisterer³ & M. Bacon⁴

On behalf of the GCIG representing AGO-OVAR, ANZGOG, EORTC-GCG, GEICO, GINECO, GOG, JGOG, MRC, NCIC-CTG, NCI-US, NSGO, RTOG, SGCTG

¹Department of Medical Oncology, University Hospital Antwerp, Edegem, Belgium; ²Department of Gynecological Oncology, Karolinska University Hospital, Sweden; ³Universitätsklinikum, Klinik für Gynäkologie und Geburtshilfe, Kiel, Germany; ⁴NCIC Clinical Trial Group, Queen's University, Kingston, Ontario, Canada

Introduction

Randomized trials are considered the definitive source of evidence for guiding decisions in clinical practice, especially when the magnitude of the expected treatment difference is at best moderate. Goals of these trials are (i) to determine the effectiveness of a treatment relative to the best current standard of care, or (ii) to assess whether a new treatment is as effective as the standard, but associated with less toxicity, cost or better quality of life. The design, execution and analysis of such trials must be based on sound scientific and ethical criteria, but it is also crucial that they have sufficient statistical power to detect a realistic and clinically important difference in overall or progression-free survival [1]. Lack of statistical power owing to small numbers of enrolled patients has been a serious problem in ovarian cancer trials in the past. Both progression-free and overall survival can be considered as important end points (although progression-free survival is also often considered as a surrogate end point for survival) and are of obvious clinical relevance for the patients, just as are quality of life or symptoms scores [2].

Optimal treatment for epithelial ovarian cancer has changed over the years both for early [3] and advanced [4] disease. Unfortunately, reaching these new standards has taken many years. This rather slow evolution has been the result of suboptimal clinical trials not having the statistical power to identify truly superior regimens, and of a lack of systematic comparisons of new agents with relevant control arms [5].

Even the platinum compounds, still the backbone of every current combination, had to undergo a meta-analysis to provide the definitive data to show they improved the survival of ovarian cancer patients [6, 7]. Moreover, despite various trials, the optimal administration of platinum compounds—as an adequately dosed single agent, used sequentially or in combination with other active agents—has not been elucidated [8–10]. Without any doubt, meta-analyses have helped to solve some of these questions, but very often meta-analyses of randomized trials in

ovarian cancer are hindered by the fact that trials included usually have different arms and may be of varying quality.

Throughout the 1980s and into the 1990s there was a tendency towards increasing the size of clinical trials in general, and in ovarian cancer in particular. A comparison of the trials directed at assessing paclitaxel with those assessing platinum or platinum combinations has made this clear [1]. The luxury of today is the availability of many new cytotoxic and biologic agents worthy of testing, but if this is to be done in a timely fashion international collaboration is a must [11].

History of the GCIG

As highlighted in the consensus statements of the second workshop on advanced ovarian cancer, a network of national or international groups might potentially facilitate the rapid evaluation of new treatment options and answer relevant questions more quickly [12].

A first stimulating experience of collaboration between Europe and Canada in the field of ovarian cancer was acquired with a paclitaxel study in patients with relapsed ovarian cancer led by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) [13]. An Ovarian Cancer Trials Intergroup Network started when European and Canadian Cooperative Groups decided to join forces in order to conduct, as rapidly as possible, a large trial in untreated patients with sufficient statistical power to confirm Gynecologic Oncology Group (GOG) trial #111 trial, after it was first reported in 1993 [14]. At that time, the analysis of GOG study #111 indicated that the combination of cisplatin and 24-h infusion paclitaxel produced a higher response rate and a longer progression-free survival than the combination of cisplatin and cyclophosphamide in women with newly diagnosed and suboptimally debulked FIGO stage III or IV epithelial ovarian cancer.

In this first trans-Atlantic intergroup trial, the following groups were involved: the European Organization for Research and Treatment of Cancer (EORTC)-Gynecological Cancer Cooperative Group, the NCIC-CTG, the Nordic Gynecological Cancer Study Group (NOCOVA) and the Scottish Gynecological Cancer Trials Group (SGCTG). This trial accrued 680 patients in 15 months completing accrual in August 1995,

*Correspondence to: Professor Dr J. B. Vermorken, Department of Medical Oncology, University Hospital Antwerp, Wilrijkstraat 10, 2650, Edegem, Belgium. Tel: +32 3 821 39 54; Fax: +32 3 825 05 64.
E-mail: Jan.B.Vermorken@uza.be

i.e. 4 months after the GOG publicly reported a highly significant survival advantage in favor of the paclitaxel combination and 4 months before these results were published in the *New England Journal of Medicine* [15]. Results of the Intergroup trial were presented at the ASCO meetings in 1997 and 1998, and the full report was published in 2000 [16]. By completing this trial in such a rapid fashion a major contribution to the international acceptance of a paclitaxel/platinum based regimen as the new standard of care eventuated. Together with the International Collaborative Ovarian Neoplasm (ICON) organization and the cooperation between a German consortium (the Arbeitsgemeinschaft Gynaekologische Onkologie, Studiengruppe Ovarialkarzinom; AGO-OVAR) and the French Groupe des Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO), this trans-Atlantic Intergroup Network was considered a giant step forward in ovarian cancer clinical research [5].

After the establishment of this Intergroup trial, regular meetings with representatives of the different cooperative groups were organized from 1995 onwards. There was a cautious start in that no official commitments were made initially, but during the meeting in 1996 there was a general agreement to maintain this 'Ovarian Cancer Trial Intergroup Network' as a readily available vehicle for future trials collaboration as well as an ongoing mechanism for communication about strategic directions of phase I/II trials within individual groups. The SWOG-ECOG-NCIC CTG Intergroup phase II trial of intraperitoneal paclitaxel, intraperitoneal cisplatin and intravenous paclitaxel was a direct spin-off of this Intergroup Network [17]. Gradually, all felt the need for a wider organization and to formalize the group's activities and so in 1997 an outline of a more formal structure was presented, statutes were accepted and the Gynecologic Cancer Intergroup (GCIG) was created (Table 1). Over the past 7 years the interest in this intergroup organization has grown, and at present GCIG has evolved to include 12 cooperative group organizations (AGO-OVAR, ANZGOG, EORTC-GCG, GEICO, GINECO, GOG, JGOG, MRC, NCIC-CTG, NSGO, RTOG, SGCTG) and NCI-US (Table 2).

Current status of the GCIG

The GCIG is an organization consisting of appointed representatives of these above-mentioned member groups performing clinical trials in gynecologic cancer. The stated aims of the GCIG are to (i) promote international collaboration, (ii) promote clinical research, (iii) perform studies in women with rare tumors, (iv) stimulate evidence-based medicine by performing high quality clinical trials and (v) support educational activities mainly by disseminating results of GCIG trials. Different working groups within GCIG are appointed to discuss items related to topics of specific interest, leading to recommendations that can be used for patients participating in trials (see below).

Cooperative member groups may appoint six representatives to attend GCIG meetings, including three principal representatives, one statistician, one data manager and one representative for translational research. GCIG is an open organization, but membership can be obtained only under certain conditions. Any international or national actively operating research group

Table 1. History of the Gynecologic Cancer Intergroup (GCIG)

Year(s)	Event	Reference
1991–1992	OV9 study (randomized study on paclitaxel dose and schedule)	[13]
1994–1995	OV10 study (randomized study of paclitaxel/cisplatin versus cyclophosphamide/cisplatin)	[16]
1995	Ovarian Cancer Trials Intergroup Network	
1996–1998	S9619 study (phase II study of i.p. paclitaxel/i.p. cisplatin/i.v. paclitaxel)	[17]
1997	Formal structure presented	
1997–1999	First GCIG trial (paclitaxel/carboplatin with or without epirubicin)	[18, 19]
2000	First official GCIG guidelines to evaluate responses to treatment in ovarian cancer	[20]

i.p., intraperitoneal; i.v., intravenous.

Table 2. Member groups of Gynecologic Cancer Intergroup

Abbreviation	Names
AGO-OVAR	Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom
ANZGOG	Australia and New Zealand Gynecological Oncology Group
EORTC-GCG	European Organization for Research and Treatment of Cancer – Gynecologic Cancer Group
GEICO	Grupo Espanol de Investigacion en Cancer de Ovario
GINECO	Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (France)
GOG	Gynecologic Oncology Group
JGOG	Japanese Gynecologic Oncology Group
MRC	Medical Research Council
NCI-US	National Cancer Institute of the US
NCIC-CTG	National Cancer Institute of Canada Clinical Trials Group
NSGO	Nordic Society of Gynecologic Oncology
RTOG	Radiation Therapy Oncology Group
SGCTG	Scottish Gynaecological Cancer Trials Group

that has completed a phase III trial in patients with gynecologic cancer on its own or which has participated as a group in at least one intergroup trial in the last 5 years, can apply for provisional membership of the GCIG by writing to the secretariat. [The GCIG has a secretariat, which presently is located at the NCIC Clinical Trials Group, Queen's University 82–84 Barrie Street, Kingston, Ontario, Canada K7L 3N6 (to the attention of Ms Bacon).] Each application is reviewed by a membership committee. Provisional membership will change to full membership after 2 years if there is active participation in at least one GCIG study during that period.

The GCIG is led by an Executive Board (since 2003), consisting of the GCIG chairpersons (chair elect, chair, past chair), secretariat manager and a representative of each member group. The Executive Board has the power to make decisions

concerning all business matters, including yearly membership dues. Each due-paying member group has one vote on the Executive Board. Changing the GCIG statutes requires a two-thirds majority vote and can only be made after circulating a proposal in writing to all members at least 3 months before the next scheduled Executive Board meeting.

General meetings usually take place twice yearly, i.e. a spring meeting in the US (connected with the ASCO meeting) and an autumn meeting in Europe (mostly connected with ECCO or IGCS) or at any other time determined upon by the Executive Board.

Working groups

Much of the GCIG activities take place in its working groups. Each member group may appoint representative(s). The following 10 working groups have been created: website (now including the webmaster), screening and prevention, translational research, radiation oncology, harmonization (i.e. related to data management/operations and statistics), classification of relapsed ovarian cancer, rare ovarian tumors, early ovarian cancer, re-

sponse/progression definition for ovarian cancer and education. Some of the working groups are dealing with long-term projects, such as the translational research group focusing on quality control, ethical issues, methodology, technology and how to collaborate on an international basis, while others have/had a specific task, such as the rare ovarian tumor working group, which organized a rare tumor web organization, or the 'response/progression' group, which formulated recommendations accepted by all member groups of the GCIG [20, 21]. Further details about the GCIG can be obtained by visiting its website (<http://ctep.cancer.gov/resources/gcig>), which is kindly sponsored by the Gynecologic Cancer Foundation (the charitable arm of the Society of Gynecologic Oncology).

Clinical trial collaborations

GCIG members have as a defining attribute, interest in inter-group clinical trials. Groups present ideas for their future studies at the semi-annual meetings and collaborative interactions develop as a result, with numerous studies completed or underway that bear the GCIG name (see Tables 3 and 4 for ovarian

Table 3. Front-line trials in advanced ovarian cancer (Gynecologic Cancer Intergroup)

Leading group	Cooperation	Design	Accrual	No. of patients	References
EORTC 55971	NCIC-CTG	Chemotherapy versus surgery upfront	Ongoing	–	–
AGO-OVAR	GINECO	TC versus TEC	Complete	1282	[18, 19]
OVAR-5					
NSGO	EORTC-GCG	TC versus TEC	Complete	887	[22–24]
OC9804	NCIC-CTG				
AGO	GINECO	TC versus TC → tpt	Complete	1308	[25]
OVAR-7					
AGO	GINECO	TC versus TCG	Complete	1721	–
OVAR-9	NSGO				
NCIC-CTG	EORTC-GCG	TC versus one sequential doublet	Ongoing		–
OV16 ^a	GEICO				
GOG 182 ^b	MRC	TC versus two triplets and two sequential doublets	Complete	>4000	[26]
	ICON				
	ANZGOG				

TC, paclitaxel + carboplatin; E, epirubicin; G, gemcitabine; tpt, topotecan.

^aOV16: sequential doublet consists of cisplatin/topotecan followed by TC.

^bGOG 182: triplets (TC + gemcitabine and TC + doxil). Sequential doublets (carboplatin/topotecan followed by TC and carboplatin/gemcitabine followed by TC).

Table 4. Second-line trials in ovarian cancer (GCIG)

Leading group	Cooperation	Design	Accrual	No. of patients	References
MRC-ICON	AGO-OVAR	Paclitaxel–platinum versus platinum-based	Complete	802	[27]
OV04					
MRC	EORTC-GCG	Early treatment based on CA 125 versus clinically indicated	Ongoing		
OV05					
AGO-OVAR	NCIC-CTG	Gemcitabine–carboplatin versus carboplatin	Complete	356	[28]
2.5	EORTC-GCG				

cancer trial examples). Impressive results of this intergroup collaboration are the increased sample size as compared with the pre-GCIG era [11] and the shortened accrual time. Most of the completed front-line trials indicated in Table 3 were accomplished within 2 years (OVAR-9 in 20 months) with a median accrual of about 1300 patients. Therefore, it can be concluded that already some of our initial goals, e.g. answering relevant questions more quickly, have been reached.

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